A Long-Acting Dolutegravir Formulation Improves Drug Safety Profile During Pregnancy

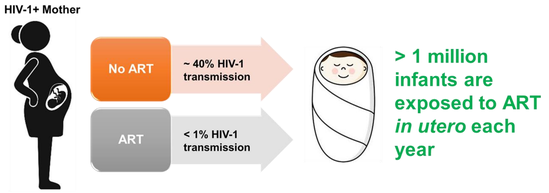
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Background

Objective: ***Safety of dolutegravir (DTG) in pregnancy***

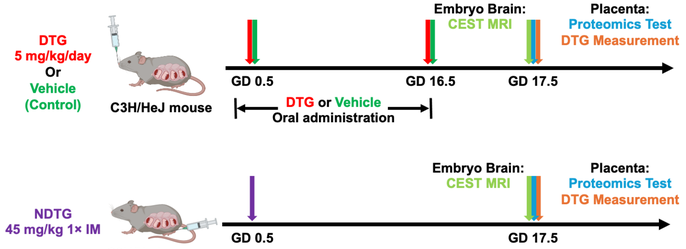


~ 45% of all adults with HIV worldwide are women of reproductive age

> 1 million infants are exposed to ART *in utero* each year

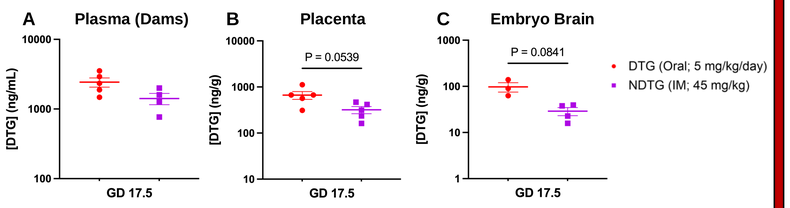
- 84% of pregnant women living with HIV-1 had access to ART in 2023 (UNAIDS 2024).
- More than 15 million people living with HIV-1 worldwide are being treated with DTG-based regimen. These include pregnant women or those of child-bearing age.
- DTG poses potential risks of fetal neurodevelopmental toxicities.

Methods

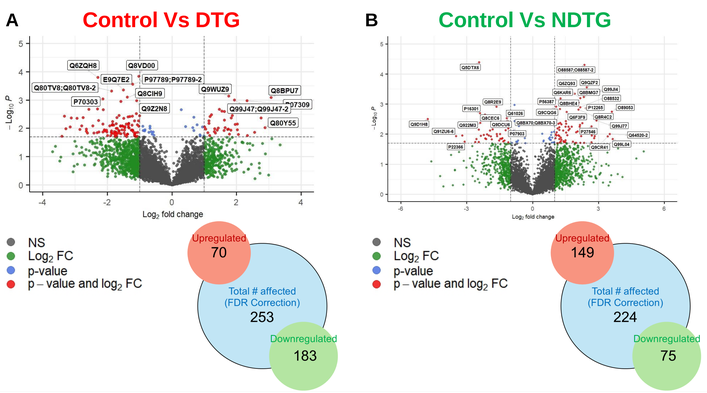


Results

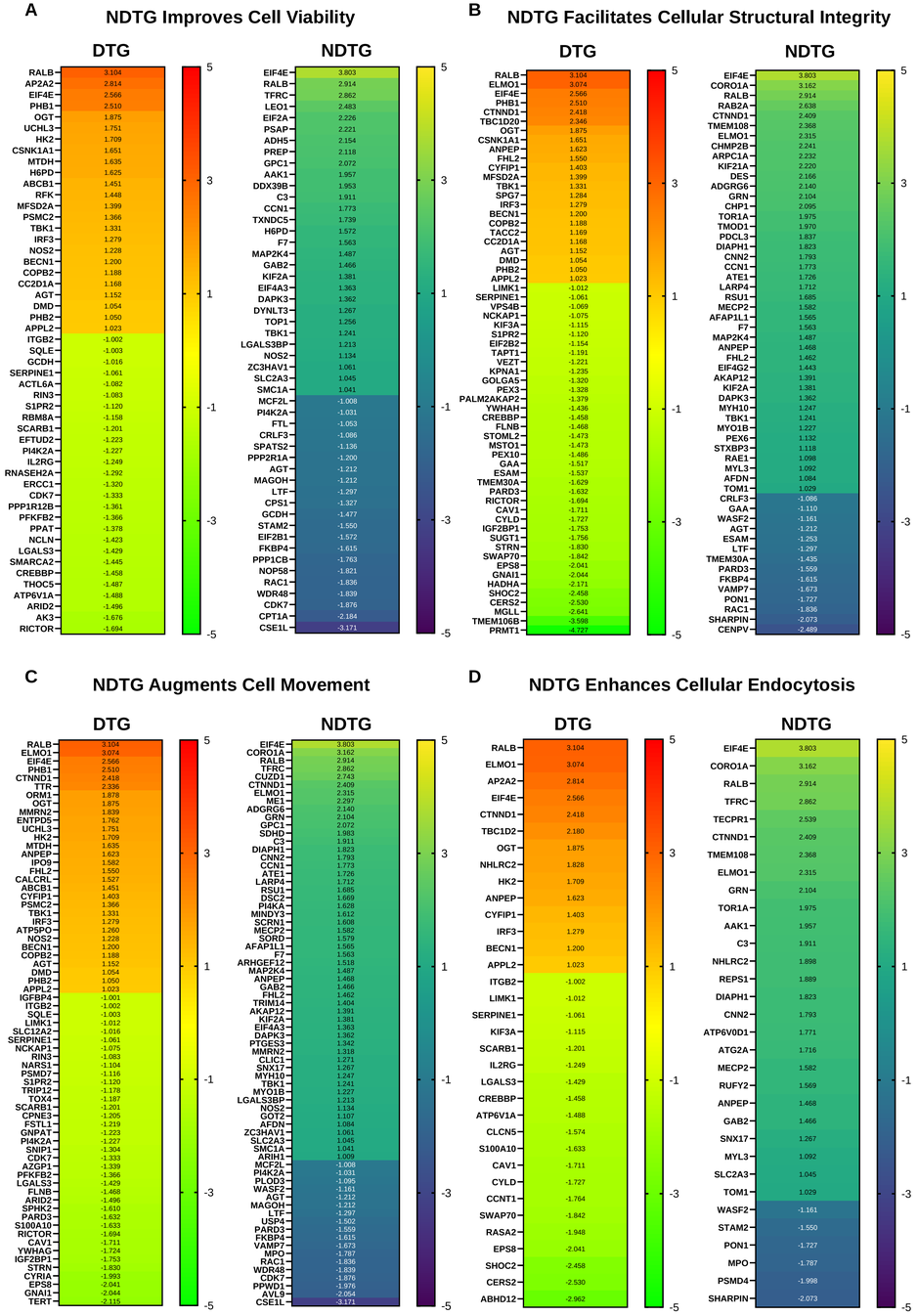
DTG-nanoformulation (NDTG) limits placental drug exposure



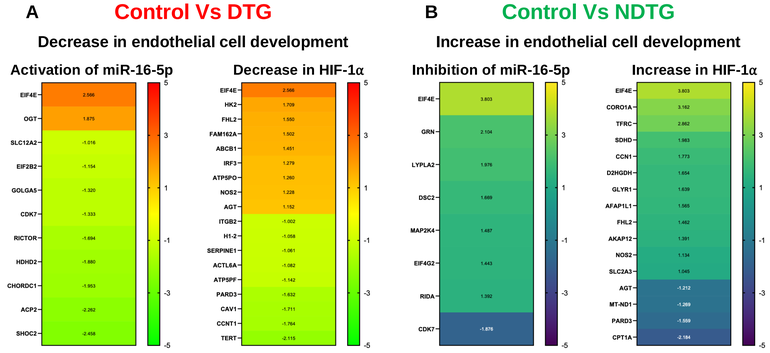
Global proteomic profiling of the placenta



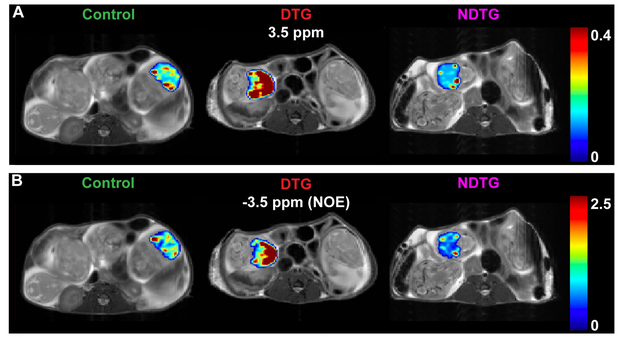
NDTG attenuates drug-induced placental cytotoxicities



NDTG ameliorates DTG-induced endothelial toxicities



NDTG prevents DTG-associated metabolites alterations in embryo brain



Conclusions

- LA DTG formulation (NDTG) achieves sustained therapeutic DTG levels in maternal blood while lowering drug exposure to the placenta and embryo brain during pregnancy.
- NDTG reduces DTG-induced impairments in placental cellular organization and functions.
- NDTG ameliorates DTG-linked impairments in endothelial cell development by inhibiting miR-16-5p and increasing HIF-1α signaling.
- NDTG mitigates DTG-induced developmental neurotoxicity in embryo brain.
- NDTG improves the safety of DTG in pregnancy.

References

- Foster EG et al., Frontiers in Pharmacology, 2023, PMID: 38149054 PMCID: PMC10750158.
- Bade AN et al., Molecular Neurobiology, 2021, PMID: 34390469 PMCID: PMC8599359.

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